Mesenchymal stem cell-based tissue regeneration is governed by recipient T lymphocytes via IFN-gamma and TNF-alpha

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Public Summary:
Bone marrow mesenchymal stem cells (BMMSCs) are non-hematopoietic multipotent stem cells capable of differentiating into both mesenchymal and non-mesenchymal cell types, including osteoblasts, adipocytes, and chondrocytes. When implanted in vivo, BMMSCs form bone and induce recipient cells to generate hematopoietic marrow components. Therefore, BMMSCs are considered to be a promising cell source for bone and hematopoietic marrow structure regeneration. To date, a variety of preclinical and clinical studies have shown that BMMSCs can generate bone and bone-associated tissues to replace damaged and diseased tissues, of which recipient cellular components may actively participate in the regeneration process. However, the detailed function of recipient cells especially immune cells in BMMSC-based tissue regeneration remains unclear. Stem cell-based regenerative medicine is a promising approach for functional tissue reconstruction, but the role of immune responses in the cell-based tissue regeneration remains unclear. Here, we showed that pro-inflammatory T cells in the recipients inhibited bone marrow mesenchymal stem cell (BMMSC)-mediated bone formation via T helper 1 (Th1) cytokine interferon (IFN)-✚induced down-regulation of runt-related transcription factor 2 (Runx-2) pathway and tumor necrosis factor (TNF)-➔ regulated BMMSC apoptosis. We revealed that TNF-➔ converted IFN-✚-activated non-apoptotic Fas to a caspase 3/8-associated apoptotic signaling in BMMSCs through inhibition of nuclear factor kappa B (NF🎁B), resulting in BMMSC apoptosis. Conversely, reduction of IFN-✚ and TNF-➔ levels at the implantation sites by systemic infusion of Foxp3+ regulatory T cells (Tregs) markedly improved BMMSC-based bone regeneration and calvarial defect repair in C57BL6 mice. For potential pharmacologic intervention, we showed that local administration of aspirin reduced levels of IFN-✚ and TNF-➔ at the implantation site and significantly improved BMMSC-based calvarial defect repair. These data collectively uncover a previously unrecognized role of recipient T cells in BMMSC-based tissue engineering and suggest a practical approach for enhancing bone regeneration by pharmacological control of local cytokines.

Scientific Abstract:
Stem cell-based regenerative medicine is a promising approach in tissue reconstruction. Here we show that proinflammatory T cells inhibit the ability of exogenously added bone marrow mesenchymal stem cells (BMMSCs) to mediate bone repair. This inhibition is due to interferon gamma (IFN-gamma)-induced downregulation of the runt-related transcription factor 2 (Runx-2) pathway and enhancement of tumor necrosis factor alpha (TNF-alpha) signaling in the stem cells. We also found that, through inhibition of nuclear factor kappaB (NF-kappaB), TNF-alpha converts the signaling of the IFN-gamma-activated, nonapoptotic form of TNF receptor superfamily member 6 (Fas) in BMMSCs to a caspase 3- and caspase 8-associated proapoptotic cascade, resulting in the apoptosis of these cells. Conversely, reduction of IFN-gamma and TNF-alpha concentrations by systemic infusion of Foxp3(+) regulatory T cells, or by local administration of aspirin, markedly improved BMMSC-based bone regeneration and calvarial defect repair in C57BL/6 mice. These data collectively show a previously unrecognized role of recipient T cells in BMMSC-based tissue engineering.